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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
ZARA, JANE J	
ART UNIT	**PAPER NUMBER**
1635	

DATE MAILED: 11/18/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/910,185	BENNETT ET AL.	
	Examiner	Art Unit	
	Jane Zara	1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *16 June 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-10,12-15,21 and 22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1, 2, 4-10, 12-15, 21, 22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: NCBI Search results.

DETAILED ACTION

This Office action is in response to the communications filed 3-23-04 and 6-16-04.

Claims 1, 2, 4-10, 12-15, 21 and 22 are pending in the instant application.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 6-16-04 has been entered.

Response to Arguments and Amendments

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Applicants' arguments are addressed below as they pertain to the instant rejections of record.

Claim Objections

Claim 2 is objected to because of the following informalities: In line 1, the "a" preceding "antisense" (of line 2) should be replaced with –an—since the "a" precedes a noun beginning with a vowel. Appropriate correction is required.

Withdrawn Rejections

Any rejections not repeated in this Office action are hereby withdrawn.

New Rejections and Rejections Necessitated by Amendments

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2, 4-10, 12-15, 21 and 22 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 1, 2, 4-10, 12-15 are drawn to compositions and methods comprising a chemically modified compound 8-50 nucleobases in length targeted to a nucleic acid molecule encoding GLI-3 of SEQ ID NO: 3 in vitro. The specification and claims teach internucleotide, nucleobase and sugar modifications of antisense oligonucleotides, including phosphorothioates, 5-methyl cytosines and 2-O-methoxyethoxy modified sugars, as well as chimeric antisense, locked nucleic acids and the chemical conjugation of various moieties to oligonucleotides, such as lipid moieties to enhance oligonucleotide uptake by target cells (see generally pp. 11-20 of the instant

specification). The genus claimed, however, encompasses any chemically modified compound 8-50 nucleobases in length and targeted to GLI-3. This genus therefore encompasses more than the modifications described on pp. 11-20 of the specification. Concise structural features that could distinguish structures or compounds within the genus (e.g. as described on pp. 11-20 or the specification) from others (e.g. oligonucleotides chemically modified with reactive groups for targeting and chemically interacting with other molecular target moieties, such as photoreactive groups, or reactive thiols, electrophiles or nucleophiles...) are missing from the claims and the instant disclosure. No common structural attributes identify the members of the genus comprising *chemically modified compounds that target GLI-3*. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general guidance is that is needed. The specification fails to teach or adequately describe the genus such that the common attributes or characteristics concisely identifying members of the proposed genus are exemplified. And because the genus is highly variant, the description provided is insufficient.

Claims 21 and 22 are drawn to methods of screening for modulation of the expression of any nucleic acid encoding GLI-3. The specification teaches the nucleic acid sequence of human GLI-3 of SEQ ID NO: 3. These claims, however, encompass the broader genus comprising any nucleic acids encoding GLI-3. This genus comprises any mutants or isoforms of GLI-3 found in any species, and/or truncations of GLI-3 (see e.g. Kalff-Suske et al, Human Molecular Genetics, 8(9): 1769-1777, 1999, especially on pp. 1770-1772 for examples of the numerous mutations of GLI-3 that have been found

to exist; see also the NCBI search results listing GLI-3 sequences from various species, including mouse and rat). The scope of claims 21 and 22 therefore includes numerous structural variants and the genus is highly variant because a significant number of structural differences between members of the genus is permitted. Concise structural features that could distinguish structures or compounds within the genus from others is missing (e.g. nucleic acids encoding the various isoforms, or mutants of GLI-3, whose modulation of expression will be screened). Specific, not general guidance is what is needed to satisfy the written description requirement for the broad genus comprising any GLI-3.

One of skill in the art would reasonably conclude that the disclosure fails to provide adequate description for the genus comprising *chemically modified compounds 8-50 nucleobases in length targeted to GLI-3 of SEQ ID NO: 3* (claims 1, 2, 4-10, 12-15) or for the genus comprising *nucleic acid molecules encoding GLI-3* (claims 21 and 22).

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1, 2, 4-15, 21 and 22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ruppert et al and Kalff-Suske et al, the combination in view of Milner and McKay insofar as the claims are drawn to compositions and methods comprising

antisense oligonucleotide compounds between 8-50 nucleotides in length which specifically target and inhibit the expression of human GLI-3 of SEQ ID NO: 3 in vitro, and which oligonucleotides further comprise a phosphorothioate internucleotide linkage modification, a 2'-O-methoxyethyl sugar modification, a 5-methyl cytosine nucleobase modification, and may optionally comprise a chimeric oligonucleotide, and which compositions further comprise a pharmaceutically acceptable diluent and a colloidal dispersion system; and which methods comprise the screening of modulators of expression of GLI-3, and which methods comprise the in vitro inhibition of expression of GLI-3 comprising the administration of antisense that specifically target GLI-3 of SEQ ID NO: 3.

Ruppert et al (Molecular & Cell. Biol., 10(10): 5408-5415, 1990, Document AI, submitted in IDS filed on July 18, 2001, Paper No. 3) teach the polynucleotide sequence encoding GLI-3, of SEQ ID NO: 3 (See figure 2 on page 5410 and the sequence alignment data provided in the Office action mailed 6-27-03).

Kalff-Suske et al (Human Molecular Genetics, 8(9): 1769-1777, 1999, Document AA, submitted in IDS filed on July 18, 2001) teach the polynucleotide sequence of GLI-3 encoded by SEQ ID NO: 3, as well as mapping of various mutations throughout GLI-3 polynucleotide sequence and their relationship to various craniofacial and limb anomalies associated with Grieg cephalopolysyndactyly syndrome (See entire document, especially text on p. 1769, text on top of p. 1771-left col., p. 1772, Table 1 on p. 1771, Accession number AJ250408 and the sequence alignment data provided in the Office action mailed 6-27-03).

Kalff-Suske et al also teach antisense oligonucleotides targeting human GLI-3 (bridging paragraph, pp. 1775-1776). The burden of establishing whether the prior art oligonucleotide has the function of inhibiting gene expression as claimed falls to applicant. See (In re Best, 562 F.2d 1252, 1255, 195 USPQ 430, 433-434 (CCPA 1977): "Where, as here, the claimed and prior art products are identical or substantially identical, or are produced by identical or substantially identical processes, the PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his claimed product... Whether the rejection is based on 'inherency' under 35 USC 102, on 'prima facie obviousness' under 35 USC 103, jointly or alternatively, the burden of proof is the same, and its fairness is evidenced b the PTO's inability to manufacture products or to obtain and compare prior art products [footnote omitted]. See also MPEP 2112: "[T]he PTO can require an applicant to prove that the prior art products do not necessarily or inherently possess the characteristics of his [her] claimed product." The MPEP at 2112 citing In re Fitzgerald 205 USPQ 594, 596 (CCPA 1980), quoting In re Best 195 USPQ 430 as per above.

The primary references of Ruppert nor Kalff-Suske et al do not teach the in vitro inhibition of GLI-3 expression using antisense oligonucleotides between 8-50 nucleobases, nor the incorporation of any modifications into the antisense oligonucleotides, nor compositions comprising pharmaceutically acceptable diluents or colloidal dispersion systems.

Milner et al (Nature Biotech. 15: 537-541, 1997) teach methods of designing and testing antisense oligonucleotides for their ability to specifically hybridize and inhibit the

expression of a target nucleic acid of known nucleotide sequence in vitro (See figure 1 on p 538 and figures 5-7 on pages 539-540).

McKay et al (USPN 6,133,246, 10-17-00) teach compositions comprising antisense oligonucleotides between 8 and 50 nucleobases in length which optionally comprise modified internucleotide linkages including phosphorothioate linkages, modified nucleobases including 5-methylcytosine, modified sugar moieties including 2'-O-methoxyethyl sugars, and wherein the antisense is optionally a chimeric oligonucleotide, and which compositions further comprise a colloidal dispersion system and a pharmaceutically acceptable carrier. McKay et al also teach the in vitro inhibition and screening of modulators (e.g. of various antisense oligonucleotides between 8-50 nucleobases that specifically hybridize with the target gene) of GLI-3 expression in vitro (see especially col. 6, line 29 through col. 15, line 10; col. 20, line 18 through col. 24, line 67; see also Tables 2 and 3 in col. 37-38).

It would have been obvious to one of ordinary skill in the art to design and utilize antisense oligonucleotides to inhibit the expression of GLI-3 of SEQ ID NO: 3 in vitro, because Milner et al and McKay teach the ability to design and assess antisense oligonucleotides for their ability to inhibit the expression of a target gene of known nucleotide sequence in vitro using routine screening assays that are well known in the art (see Milner at pages 539-540 and McKay at col. 6-15). It would have been obvious to one of ordinary skill in the art to target and inhibit the expression of GLI-3 in vitro comprising the administration of antisense oligonucleotides between 8-50 nucleobases because Milner teaches methods of designing and assessing antisense

oligonucleotides between 8-50 nucleobases for their ability to target and inhibit the expression of a known target gene in vitro, and both Ruppert and Kalff-Suske et al teach the nucleic acid sequence encoding GLI-3 (of SEQ ID NO: 3). One of ordinary skill in the art would have been motivated to utilize such a method of finding optimal antisense oligonucleotides between 8-50 nucleobases which best target and inhibit GLI-3 expression in order to study this target molecule's role in various cellular processes involved in craniofacial and limb development because GLI-3's role in development had been taught previously by Kalff-Suske et al and Ruppert et al teach the amplification of GLI-3 in tumors (see e.g. Ruppert et al in the abstract and introduction on p. 5408). One of ordinary skill in the art would have expected that the methods of designing and assessing antisense oligonucleotides for inhibiting a target gene of known sequence, which were taught by Milner et al, and also taught by McKay to be routine for a previously characterized target gene, would successfully be used to identify numerous antisense oligonucleotides (between 8-50 nucleobases) for the in vitro inhibition of GLI-3 expression of SEQ ID NO: 3. One of ordinary skill in the art would have been motivated to incorporate the nucleobase, internucleotide linkage and sugar modifications, as well as chimeric structures, into antisense oligonucleotides because such modifications (including 5-methyl cytosine, 2'-O-methoxyethyl and phosphorothioate linkages) have been taught previously by McKay et al to increase target binding, cellular uptake and antisense stability. One of ordinary skill in the art would have been motivated to utilize pharmaceutically acceptable diluents in order to achieve the appropriate concentration of antisense oligonucleotides for administration to

target cells in a manner which is compatible for maintaining cellular integrity and antisense stability and one would have been motivated to utilize colloidal dispersions in order to enhance antisense stability and cellular delivery of antisense, as taught by McKay et al. One of ordinary skill in the art would have expected that the delivery of modified antisense oligonucleotides to target cells harboring GLI-3, which antisense specifically hybridize with the target nucleic acid encoding GLI-3 (i.e. of SEQ ID NO: 3), would lead to inhibition of expression of GLI-3 in vitro.

Therefore, the invention as a whole would have been prima facie obvious to one of ordinary skill at the time the invention was made.

Applicant's arguments filed 3-23-04 have been fully considered but they are not persuasive. Applicants argue that the prior art rejection does not properly for several reasons. Applicants argue that the antisense primers taught by Kalff-Suske et al do not specifically hybridize to glioma associate oncogene 3 (GLI-3) of SEQ ID NO: 3 because Kalff-Suske teach mutations directly involved in various conditions, and associated with aberrant expression of glioma associated oncogene 3. Contrary to Applicants' assertions, the antisense disclosed by Kalff-Suske et al, despite the major emphasis of the article, are antisense oligonucleotides that specifically hybridize and inhibit the expression of glioma associated oncogene 3 in vitro. Whether they be used for other uses (such as PCR amplification) or not does not alter their ability to specifically hybridize to the target gene glioma associated oncogene 3. And absent evidence to the contrary, these antisense oligonucleotides possess the ability to specifically hybridize to the target gene and inhibit its expression in vitro.

Applicants argue that the 103 rejection is improper because Ruppert and Kalff-Suske do not specifically disclose the inhibition of the target gene glioma associated oncogene 3 in vitro using antisense. Applicants are correct that the primary references do not explicitly disclose inhibition of expression of GLI-3 in vitro using antisense, but, contrary to Applicants' assertions, the 103 rejection is proper because both Ruppert and Kalff-Suske provide the nucleotide sequence of the target glioma associated oncogene 3 gene, as well as the motivation to inhibit its expression because of its involvement in various pathological conditions. Ruppert and Kalff-Suske both provide the polynucleotide sequence that enable the motivated artist of ordinary skill in the art to design and assess antisense oligonucleotides for their ability to inhibit the expression of glioma associated oncogene 3 in vitro. This general methodology was taught previously by Milner and McKay for any previously characterized target gene of interest and therefore, contrary to Applicants' assertions, it was routine to utilize the general technique taught by Milner and McKay, and used routinely by others in the field of antisense, to design antisense oligonucleotides and test them for their ability to inhibit the expression of glioma associated oncogene 3 in vitro. Furthermore, it would be reasonably expected that, knowing the target gene's nucleotide sequence, and knowing the routine experimental procedures taught by Milner and McKay to test the ability of any antisense to target and inhibit the expression of any target gene in vitro, candidate antisense oligonucleotides are routinely found that successfully inhibit the target gene's expression in vitro. Therefore, on of ordinary skill in the art would have been motivated to target and inhibit glioma associated oncogene 3 expression because of this

oncogene's involvement in various cellular anomalies, and one of ordinary skill in the art would have reasonably expected to design, test and identify antisense that specifically target and inhibit this target gene's expression in vitro using the routine techniques described in the Milner and McKay references.

Conclusion

Certain papers related to this application may be submitted to Art Unit 1635 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is **703-872-9306**. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Jane Zara** whose telephone number is **(571) 272-0765.** If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, John LeGuyader, can be reached on (571) 272-0760. Any inquiry regarding this application should be directed to the patent analyst, Katrina Turner, whose telephone number is (571) 272-0564. Any inquiry of a general nature or relating to the

status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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